FILE 'MEDLINE, EMBASE, BIOSIS' ENTERED AT 14:39:48 ON 06 DEC 2001

E NEIRYNCK/AU

E NEIRYNCK S/AU

L1	0	S	E3 AND E4
L2	0	S	E3 ORB E4
L3	17	S	E3 OR E4
L4	12563	S	INFLUENZA VACCINE
L5	124877	S	M2
L6	40	S	L4 AND L5
L7	27		DUP REM L6 (13 DUPLICATES REMOVED)
L8	1344	S	PASSIVE IMMUNITY
L9	1114437	S	LENGTH OR DURATION
L10	60	S	L8 AND L9
L11	78	S	L8 AND L9
L12	43		DUP REM L11 (35 DUPLICATES REMOVED)
L13	8	S	L4 AND L8
L14	688	S	L4 AND SUBUNIT
L15	1263606	S	REVIEW
L16	4	S	L14 AND L5

FILE 'MEDLINE' ENTERED AT 15:18:48 ON 06 DEC 2001

L17	38100	S	ANIMAL MODEL
L18	28	S	L4 AND L17
L19	2	S	L18 AND L15

L17 ANSWER 1 OF 3 MEDLINE
ACCESSION NUMBER: 2003115479 IN-PROCESS
DOCUMENT NUMBER: 22515849 PubMed ID: 12628550
TITLE: N-terminus of M2 protein could induce antibodies with inhibitory activity against **influenza** virus replication.
AUTHOR: Liu Wanli; Li Hua; Chen Ying Hua
CORPORATE SOURCE: Laboratory of Immunology, Research Centre for Medical Science and Department of Biology, Tsinghua University, Protein Science Laboratory of MOE, 100084, Beijing, PR China.
SOURCE: FEMS IMMUNOLOGY AND MEDICAL MICROBIOLOGY, (2003 Mar 20) 35 (2) 141-6.
Journal code: 9315554. ISSN: 0928-8244.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20030312
Last Updated on STN: 20030312

AB New **influenza** vaccines have been designed based on the fact that the extracellular domain of M2 protein (**M2e**) is nearly invariant in all **influenza** A strains. To clarify which exact region of **M2e** could induce antibodies with inhibitory activities against **influenza** virus replication, four overlapping peptides covering **M2e** were synthesized and then coupled to the carrier protein bovine serum albumin through the cysteine of the peptides. After a vaccination course, all these four peptide vaccines could induce high levels of rabbit antibodies with predefined peptide specificity (antibody dilution: 1:6400-1:25600). Besides, the anti-N-terminal antibodies (AS2) reacted strongly with **M2e**, and reacted weakly with the middle part and C-terminus of **M2e**. The MDCK assay for cytopathic effect proved that antibodies recognizing the N-terminus of **M2e** could obviously inhibit replication of **influenza** A virus (A/wuhan/359/95) and **influenza** B virus (B/wuhan/321/99) in vitro in a dose-dependent manner, while antibodies recognizing the middle part and the C-terminus of **M2e** did not show such significant inhibitory activities. Sequence analysis indicates that the first nine N-terminal amino acid residues of **M2e** are extremely conservative. Just this region containing the first nine amino acid residues could induce antibodies with inhibitory activity against **influenza** A and **influenza** B virus replication, suggesting that the N-terminus of **M2e** may contain an epitope that could induce inhibitory antibodies against **influenza** virus replication in vitro.

L7 ANSWER 5 OF 27 MEDLINE
ACCESSION NUMBER: 2001253841 MEDLINE
DOCUMENT NUMBER: 21250279 PubMed ID: 11351773
TITLE: Managing influenza: amantadine, rimantadine and beyond.
AUTHOR: Fleming D M
CORPORATE SOURCE: Northfield Health Centre, Birmingham B31 1QT, UK.
SOURCE: INTERNATIONAL JOURNAL OF CLINICAL PRACTICE, (2001 Apr) 55 (3) 189-95. Ref: 62
Journal code: CVT; 9712381. ISSN: 1368-5031.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010604
Last Updated on STN: 20010604
Entered Medline: 20010531

AB Amantadine and rimantadine are effective in the treatment and prophylaxis of influenza A. Neither drug, however, has achieved widespread acceptance because of the rapid development of viral resistance, their lack of activity against influenza B and, in the case of amantadine, adverse events. Complete cross-resistance occurs with these compounds and is associated with a single nucleotide change in the M2 protein. Resistant variants are transmissible and fully pathogenic. Zanamivir is the first widely approved neuraminidase inhibitor for the treatment of influenza. It is delivered directly to the primary site of viral replication, the respiratory tract, and is well tolerated and effective in the treatment of both influenza A and B. Data in prophylaxis are also encouraging. During the extensive clinical programme no evidence for the emergence of drug-resistant strains with acute therapy was found. Zanamivir represents a significant advance over older agents in the management of influenza A and B.

L Number	Hits	Search Text	DB	Time stamp
1	7	influenza with antigen with (purify or isolate)	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/12/06 17:31
2	14	influenza with antigen with ELISA	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/12/06 17:32
3	0	influenza adj virus adj antigen with ELISA	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/12/06 17:32
4	4417	influenza and antigen	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/12/06 17:33
5	876	influenza with antigen	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/12/06 17:33
6	107	influenza adj antigen	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/12/06 17:33
-	475	influenza adj vaccine	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/12/06 13:44
-	400885	M2	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/12/06 13:44
-	51	(influenza adj vaccine) and M2	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/12/06 17:27
-	13979	(fusion adj protein) or (fusion adj polypeptide)	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/12/06 14:31
-	2	(influenza adj vaccine) and M2 and ((fusion adj protein) or (fusion adj polypeptide))	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/12/06 17:08
-	0	neirynck.in	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/12/06 14:35
-	844	Jou.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/12/06 14:34

-	2	(influenza adj vaccine) and Jou.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/12/06 14:34
-	16	neirynck.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/12/06 14:35
-	45	slepushkin.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/12/06 17:08
-	1	slepushkin.in. and influenza	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM TDB	2001/12/06 17:09

Monoclonal antibodies: their importance to surgeons.

Estabrook A, Mesa-Tejada R.

Columbia University, Columbia Presbyterian Medical Center, New York, NY 10032.

A tremendous technological advance occurred in 1975 when a method was developed to fuse two cells producing a "hybridoma" which secretes a single clone of antibody, having one immunoglobulin (Ig) class, one structure, one affinity, and one specificity for an antigenic determinant. Because monoclonal antibodies are more precise reagents than conventional antisera they open new doors to diagnosis and therapy of disease, and they are useful tools in research. The pathologist uses monoclonals in immunocytochemistry to determine tumor type; the surgeon uses monoclonals for immunosuppression in renal transplantation; the immunologist uses monoclonals to decipher cellular and humoral interactions that could not be appreciated with polyclonal reagents. This review outlines the background of monoclonal antibodies and some of their clinically important uses, both in vitro and in vivo. We also project into the future and describe chimeric antibodies and their possible uses.

Publication Types:
- Review
- Review, Tutorial

PMID: 2487250 [PubMed - indexed for MEDLINE]

1: Protein Sci 1998 Nov;7(11):2359-73

pH-induced conformational changes of membrane-bound influenza hemagglutinin and its effect on target lipid bilayers.

Gray C, Tamm LK.

Department of Molecular Physiology and Biological Physics, University of Virginia Health Sciences Center, Charlottesville 22906-0011, USA.

Influenza virus hemagglutinin (HA) has served as a paradigm for both pH-dependent and -independent viral membrane fusion. Although large conformational changes were observed by X-ray crystallography when soluble fragments of HA were subjected to fusion-pH conditions, it is not clear whether the same changes occur in membrane-bound HA, what the spatial relationship is between the conformationally changed HA and the target and viral membranes, and in what way HA perturbs the target membrane at low pH. We have taken a spectroscopic approach using an array of recently developed FTIR techniques to address these questions. Difference attenuated total reflection FTIR spectroscopy was employed to reveal reversible and irreversible components of the pH-induced conformational change of the membrane-bound bromelain fragment of HA, BHA. Additional proteolytic fragments of BHA were produced which permitted a tentative assignment of the observed changes to the HA1 and HA2 subunits, respectively. The membrane-bound HA1 subunit undergoes a reversible conformational change, which most likely involves the loss of a small proportion of beta-sheet at low pH. BHA was found to undergo a partially reversible tilting motion relative to the target membrane upon exposure to pH 5, indicating a previously undescribed hinge near the anchoring point to the target membrane. Time-resolved amide H/D exchange experiments revealed a more dynamic (tertiary) structure of membrane-bound BHA and its HA2, but not its HA1, subunit. Finally BHA and, to a lesser degree, HA1 perturbed the lipid bilayer of the target membrane at the interface, as assessed by spectral changes of the lipid ester carbonyl groups. These results are discussed in the context of a complementary study of HA that was bound to viral membranes through its transmembrane peptide (Gray C, Tamm LK, 1997, Protein Sci 6:1993-2006). A distinctive role for the HA1 subunit in the conformational change of HA becomes apparent from these combined studies.

PMID: 9828002 [PubMed - indexed for MEDLINE]

L8 ANSWER 9 OF 12 MEDLINE
ACCESSION NUMBER: 95088592 MEDLINE
DOCUMENT NUMBER: 95088592 PubMed ID: 7527837
TITLE: Functional reconstitution in lipid vesicles of **influenza** virus **M2** protein expressed by baculovirus: evidence for proton transfer activity.
AUTHOR: Schroeder C; Ford C M; Wharton S A; Hay A J
CORPORATE SOURCE: Division of Virology, National Institute for Medical Research, Mill Hill, London, U.K.
SOURCE: JOURNAL OF GENERAL VIROLOGY, (1994 Dec) 75 (Pt 12) 3477-84.
Journal code: 0077340. ISSN: 0022-1317.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 19950126
Last Updated on STN: 19960129
Entered Medline: 19950113

AB The **influenza** virus **M2** protein was expressed from a recombinant baculovirus in Spodoptera frugiperda Sf9 cells, purified and reconstituted into artificial membrane vesicles. The specific inhibitor amantadine overcame the toxic activity of the protein and boosted the rate of **M2** synthesis by a factor of 10, allowing yields of about 1 mg of purified **M2** protein per g of Sf9 cells. **M2** protein expressed in this system was phosphorylated and palmitoylated and displayed properties similar to the authentic virus protein. Purified wild-type **M2** protein and an amantadine-resistant mutant **M2** (**M2** delta) with a deletion in the trans-membrane domain (amino acids 28 to 31) were incorporated into lipid vesicles, which were loaded with the fluorescent pH indicator pyranine. On imposition of an ionic gradient, **M2** caused a decrease in intravesicular pH, which was susceptible to inhibition by 0.1 to 1 microM-rimantadine or N-ethyl-rimantadine. **M2** delta behaved similarly but exhibited the expected drug resistance. These experiments indicate that isolated **M2** functions as an ion channel and demonstrates in vitro **M2**-mediated proton translocation.

L8 ANSWER 10 OF 12 MEDLINE
ACCESSION NUMBER: 94118441 MEDLINE
DOCUMENT NUMBER: 94118441 PubMed ID: 8289394
TITLE: Rescue of vector-expressed fowl plague virus hemagglutinin in biologically active form by acidotropic agents and coexpressed **M2** protein.
AUTHOR: Ohuchi M; Cramer A; Vey M; Ohuchi R; Garten W; Klenk H D
CORPORATE SOURCE: Institut fur Virologie, Philipps-Universitat Marburg, Germany.
SOURCE: JOURNAL OF VIROLOGY, (1994 Feb) 68 (2) 920-6.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199402
ENTRY DATE: Entered STN: 19940312
Last Updated on STN: 19950206
Entered Medline: 19940218

AB The hemagglutinin of the Rostock strain of fowl plague virus was expressed in CV-1 cells by a simian virus 40 vector, and its stability in the exocytotic transport process was examined by a fusion assay. A 50-fold increase in the fusion activity of the hemagglutinin was observed when expression occurred in the presence of ammonium chloride, Tris-HCl, or high doses of amantadine. When chloroquine, another acidotropic agent, was used, the hemagglutinin exposed at the cell surface had to be activated by trypsin, because intracellular cleavage was inhibited by this compound. Hemagglutinin mutants resistant to intracellular cleavage did not require acidotropic agents for full expression of fusion activity, when treated with trypsin after arrival at the cell surface. These results indicate that fowl plague virus hemagglutinin expressed by a simian virus 40 vector is denatured in the acidic milieu of the exocytotic pathway and that cleavage is a major factor responsible for the pH instability. Coexpression with the **M2** protein also markedly enhanced the fusion activity of the hemagglutinin, and this effect was inhibited by low doses of amantadine. These results support the concept that **M2**, known to have ion channel function, protects the hemagglutinin from denaturation by raising the pH in the exocytotic transport system. The data also stress the importance of acidotropic agents or coexpressed **M2** for the structural and functional integrity of vector-expressed hemagglutinin.

L8 ANSWER 11 OF 12 MEDLINE
ACCESSION NUMBER: 94009630 MEDLINE
DOCUMENT NUMBER: 94009630 PubMed ID: 8405397
TITLE: Assembly of eukaryotic class III (N-out, C-in) membrane proteins into the Escherichia coli cytoplasmic membrane.
AUTHOR: Hennessey E S; Hashemzadeh-Bonehi L; Hunt L A; Broome-Smith J K
CORPORATE SOURCE: Microbial Genetics Group, School of Biological Sciences, University of Sussex, Falmer, Brighton, UK.
SOURCE: FEBS LETTERS, (1993 Sep 27) 331 (1-2) 159-61.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 19970203
Entered Medline: 19931026

AB Class III membrane proteins lack cleavable signal peptides but adopt an N-out, C-in topology with respect to their native membranes. We have analysed the fate of two eukaryotic class III plasma membrane proteins, human erythrocyte glycophorin C and **influenza** A virus **M2** protein, in Escherichia coli. The N-terminal domains of both proteins were efficiently localised to the extracytoplasmic side of the bacterial cytoplasmic membrane. When beta-lactamase was fused to the C-terminus of glycophorin C it was localised to the cytoplasm, and protease treatment of spheroplasts caused a reduction in size of the **fusion protein** consistent with glycophorin C adopting its native topology in E. coli.